PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PU4675WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 03/05953	International filing date *(day/month/year)* 25.02.2003	Priority date *(day/month/year)* 01.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D239/42		
Applicant SMITHKLINE BEECHAM CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.09.2003	11.05.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Frelon, D Telephone No. +49 30 25901-312

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/05953

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-161 as originally filed

Claims, Numbers

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 18-20

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 18-20

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17,21-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17,21-23
Industrial applicability (IA)	Yes:	Claims	1-17,21-23
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claims 18 to 20 are directed to a method of treatment of the human or animal body by surgery or therapy. They relate to subjet-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34 (4) (a)(i) PCT).
Under the terms of Rule 39.1(iv) PCT, the IPEA is not required to carry out an examination of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. Cited documents

D1: WO 0246176 (intermediate document)
D2: Synthesis (1997), (7), 778-782
D3: Journal Of Medicinal Chemistry, 43(4), 527-550
D4: Toxicology In Vitro, 12(6), 619-632
D5: Chemistry And Biology, Current Biology, 4(12), 909-918
D6: Bioorganic & Medicinal Chemistry Letters (2001), 11(22), 2959-2962
D7: WO 0140207

2. Novelty

2.1 The intermediate document D1 is relevant for the purposes of Rules 33.1 c, 64.3 and 70.10 PCT, but since the priority documents are not available at the time of establishing the written opinion, they are not taken into account. It is based on the assumption that all claims enjoy priority rights from the filing date of the priority document(s). If it later turns out that this assumption is not correct, the intermediate document in the International Search Report (ISR) could become relevant in order to

assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.
If the priority date is not valid for the complete claimed subject-matter, this document may become relevant prior art in a possible regional/national phase.

2.2 Compounds 1e-1h of D2 differ by the CONH-R_2 end corresponding to the present R_3 end. R_3 is a (evt. subst.) heteroaryl group whereas R_2 is a substituted phenyl group and an additional difference is in the intercalation of the amide link in the compounds of D2.
With the compound GW2433, D3 discloses a similar difference for a PPAR activator. D4-D7 disclose a close state of the art with a principal structural difference wherein a (hetero)aromatic ring (corresponding ot the present R3) is not directly connected to the nitrogen atom like in the present application but *via* a spacer which can be a carbonyl amine link, a carbonyl link or a methyl carbonyl link.

3. Inventive step

3.1 According to the description, the problem underlying the present application is to provide compounds that activate human peroxisome proliferator activated receptors (hPPARs). All compounds of the cited prior art are also PPAR modulators.

3.2 D2 to D4 teaches that a common structure is necessary for the activity. A scheme thereof, given in D4, page 629, proposes a structural template for peroxisome proliferators showing the likely structural requirements for activity. It appears that the compounds according to the present application fulfil these requirements. D5 to D7 confirm that scheme. The skilled person knows consequently that the substitution pattern on the nitrogen atom is allowed to vary to some extent provided that (hetero)aromatic groups are present at this end of the molecule. The skilled person expects therefore that, at least qualitatively, the presently claimed compounds act as PPAR modulators.

3.3 Binding assays are described on pages 160 and following. But no specific result is given except the confirmation that "the examplified compounds of this invention are agonists of at least one hPPAR subtype". It is noted that this statement does not cover all the claimed compounds but only the claimed ones which represent a relatively

narrow illustration of the claimed scope.

The **technical problem** underlying the application in suit (Article 33 (3) PCT, Rule 5.1(a)(iii) PCT) to provide further compounds with the alleged activity is therefore solved in an obvious manner. With regard to the requirement of inventive step (Article 33 (3) PCT), the Applicant should have shown that the **characterising feature** which distinguishes the present invention is responsible for an unexpected effect in view of the teaching of the state or the art available to a skilled person.

4. Industrial applicability

4.1 No objection re industrial applicability of claims 1-17, 21-23 arises insofar the claimed compounds would exhibit the alleged unexpected pharmacological properties (Article 33 (4) PCT).

4.2 For the assessment of the present claims 18-20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treament and the use of such a compound for the manufacture of a medicament for a new medical treatment.